

Applicants: Arlindo L. Castelhano, et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 2

Amendments to the Claims

Please cancel claims 125 and 132 without prejudice to applicants' right to pursue the subject matter of these claims in this or a related application.

Please amend claims 76-99, 105, 110, 124 and 133 and add new claims 134-135 under the provisions of 37 C.F.R. §1.121, as set forth in the Federal Register on June 30, 2003 as follows:

Applicants: Arlindo L. Castelhano et al.

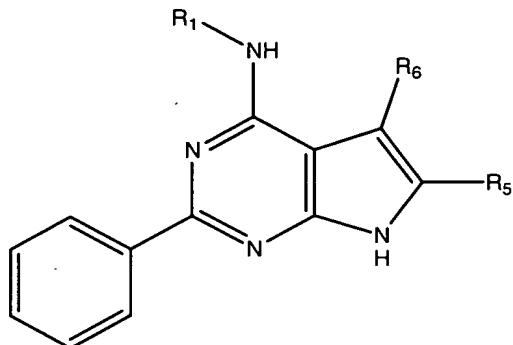
Serial No.: 09/728,616

Filed : December 1, 2000

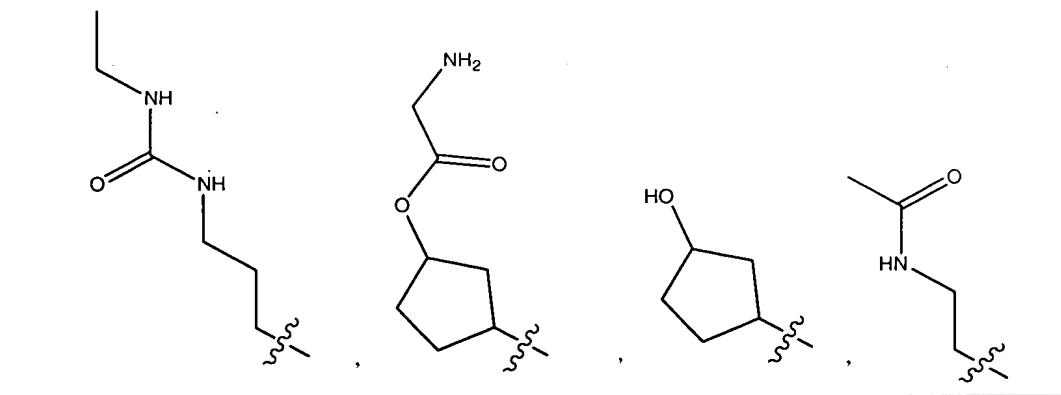
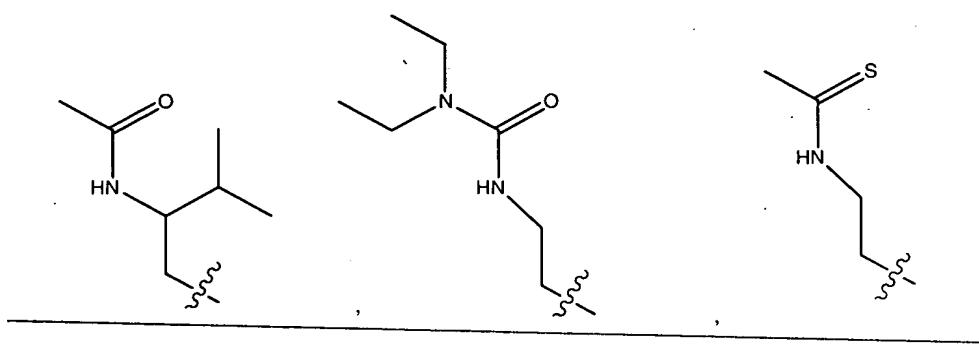
Page 3

Claims 1-75. (Canceled)

76. (Currently Amended) A compound having the structure:



wherein R₁ is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2-methyl,

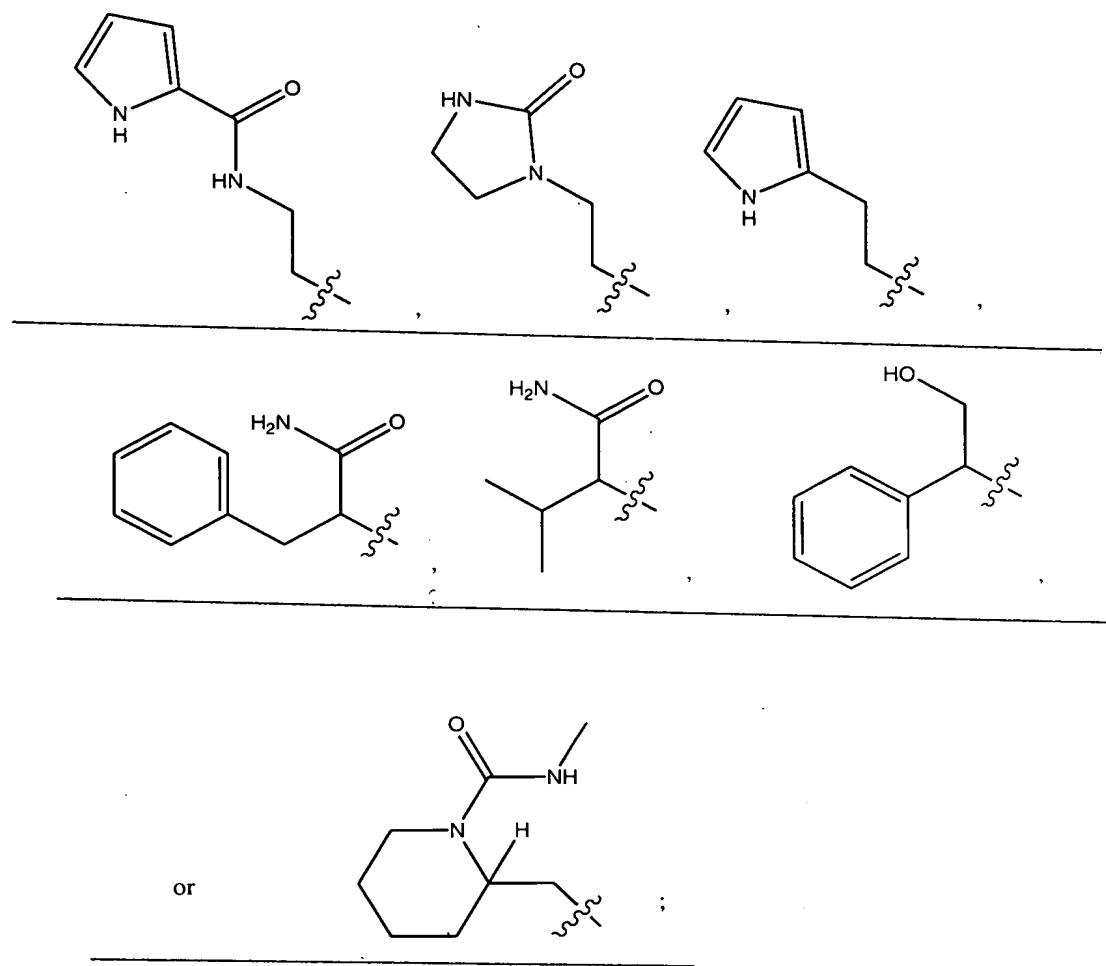


Applicants: Arlindo L. Castelhano et al.

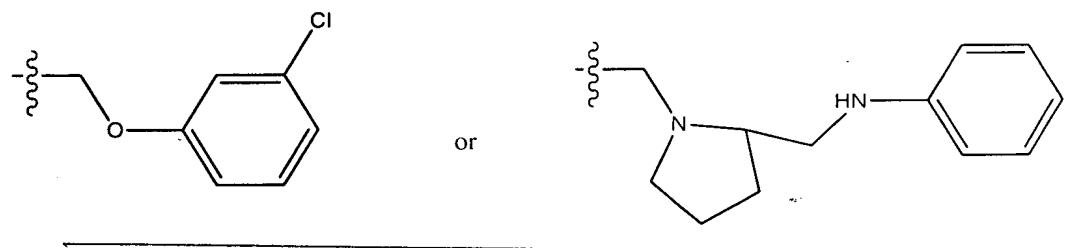
Serial No.: 09/728,616

Filed : December 1, 2000

Page 4



wherein R_5 is H, CH_3 , phenyl, and R_6 are independently H, substituted or unsubstituted alkyl, or aryl.



wherein R_6 is H or CH_3 .

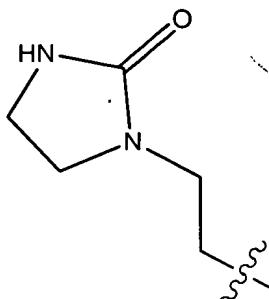
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 5

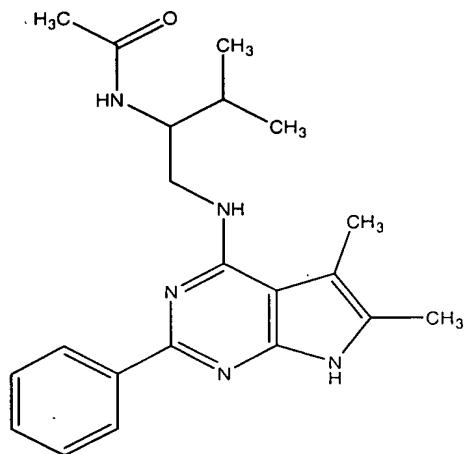
and wherein when R1 is



R5 is phenyl.

or a pharmaceutically acceptable salt thereof.

77. (Currently amended) The compound of claim 76, having the structure:



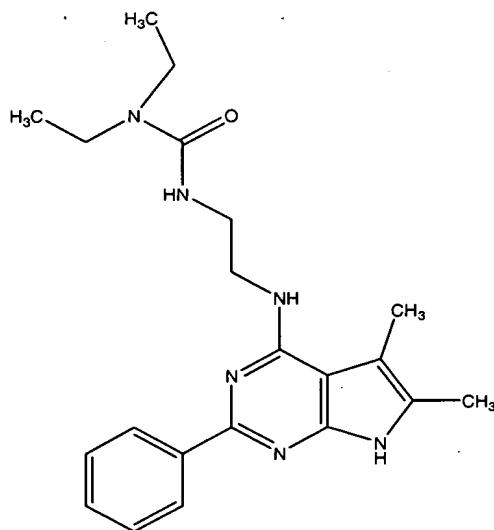
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

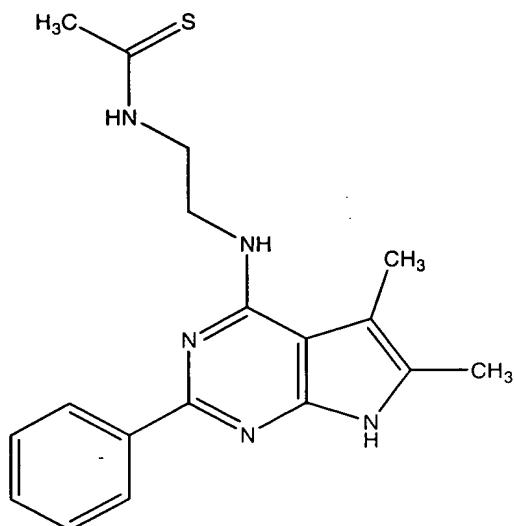
Filed : December 1, 2000

Page 6

78. (Currently amended) The compound of claim 76, having the structure:



79. (Currently amended) The compound of claim 76, having the structure:



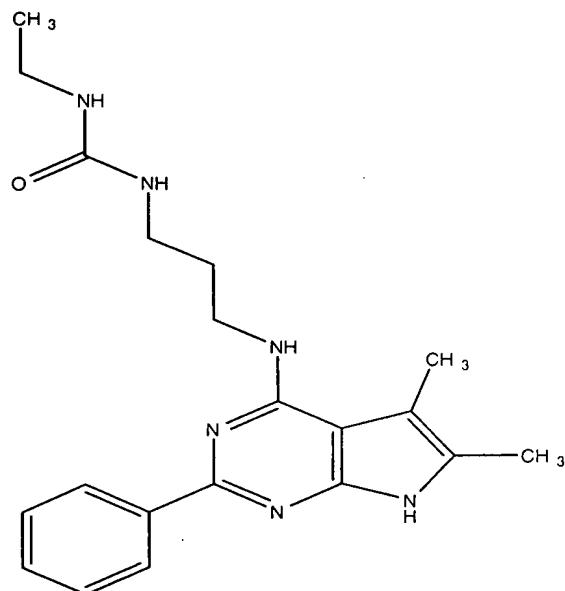
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

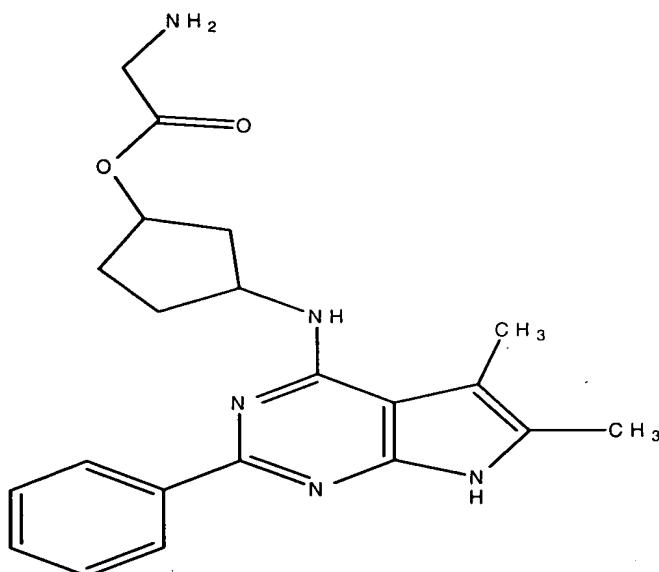
Filed : December 1, 2000

Page 7

80. (Currently amended) The compound of claim 76, having the structure:



81. (Currently amended) The compound of claim 76, having the structure:



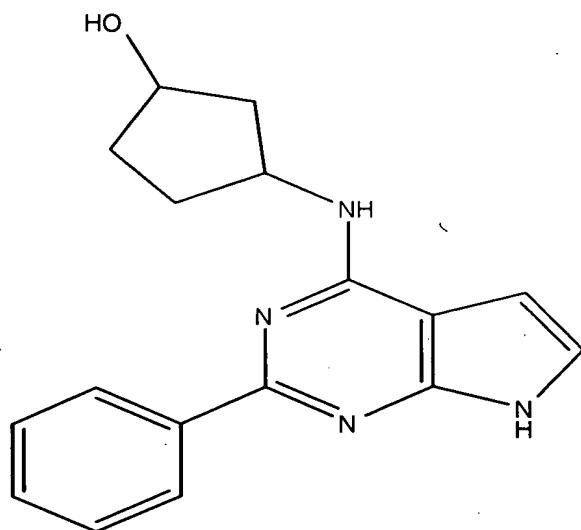
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

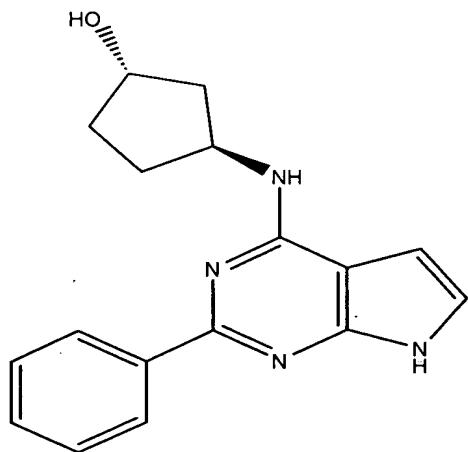
Filed : December 1, 2000

Page 8

82. (Currently amended) The compound of claim 76, having the structure:



83. (Currently amended) The compound of claim 82, having the structure:



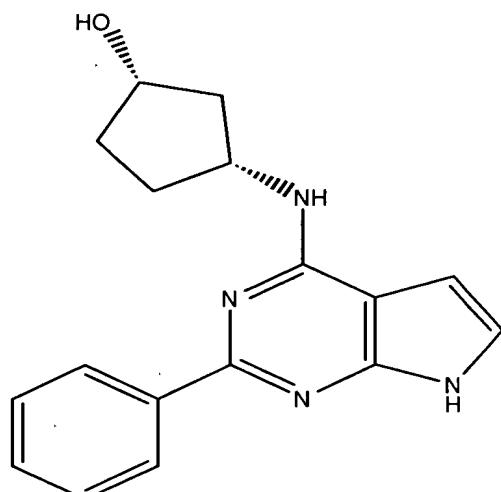
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

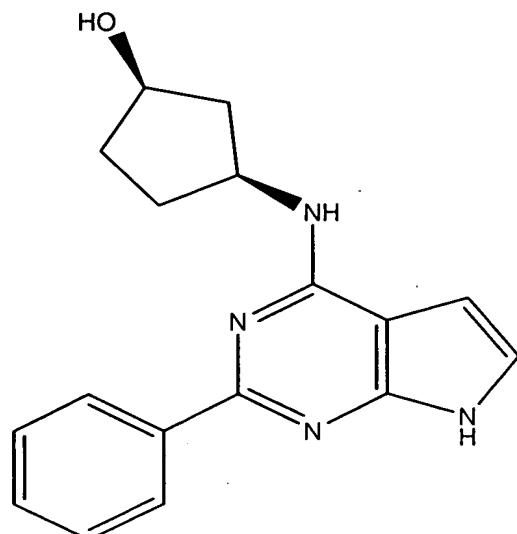
Filed : December 1, 2000

Page 9

84. (Currently amended) The compound of claim 82, having the structure:



85. (Currently amended) The compound of claim 82, having the structure:



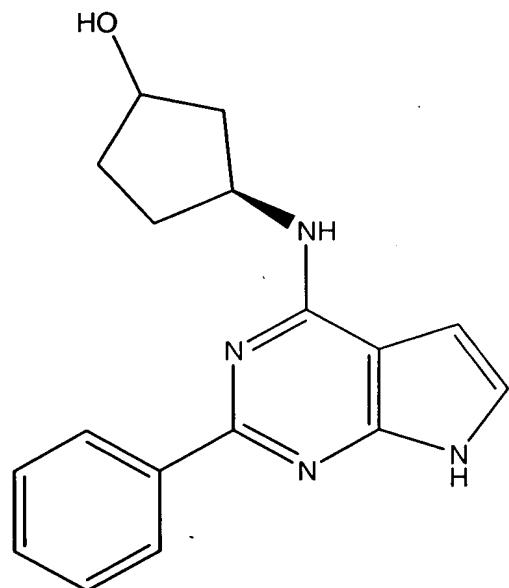
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

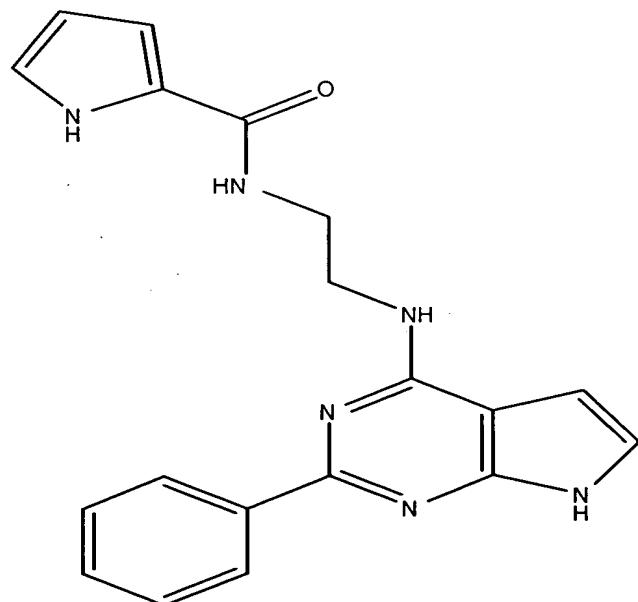
Filed : December 1, 2000

Page 10

86. (Currently amended) The compound of claim 82, having the structure:



87. (Currently amended) The compound of claim 76, having the structure:



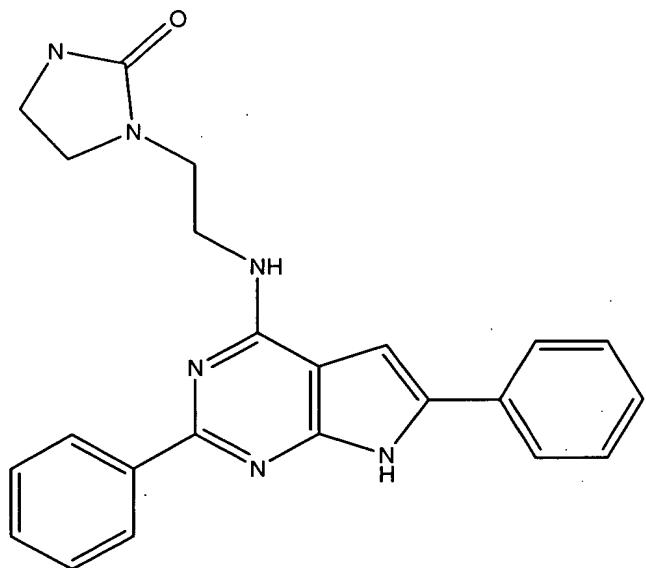
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

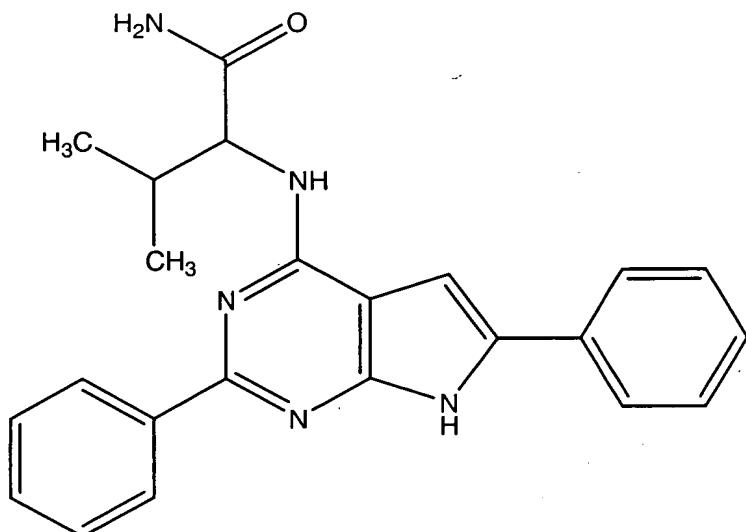
Filed : December 1, 2000

Page 11

88. (Currently amended) The compound of claim 76, having the structure:



89. (Currently amended) The compound of claim 76, having the structure:



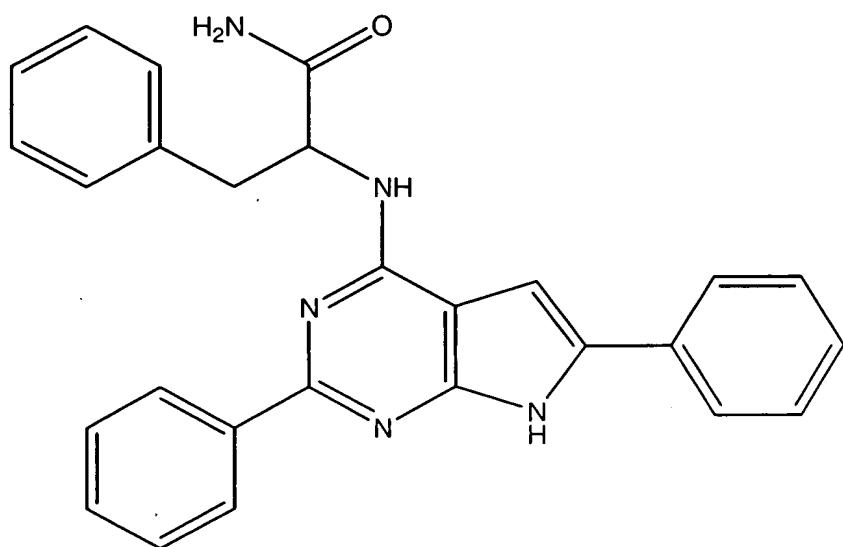
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

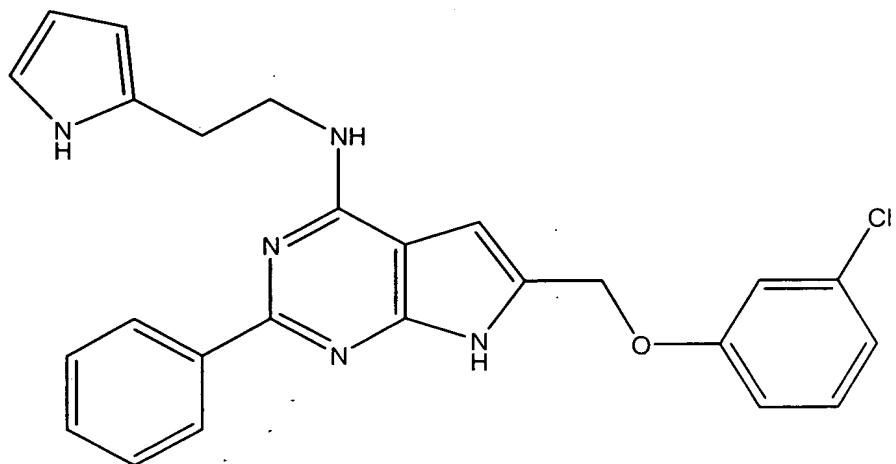
Filed : December 1, 2000

Page 12

90. (Currently amended) The compound of claim 76, having the structure:



91. (Currently amended) The compound of claim 76, having the structure:



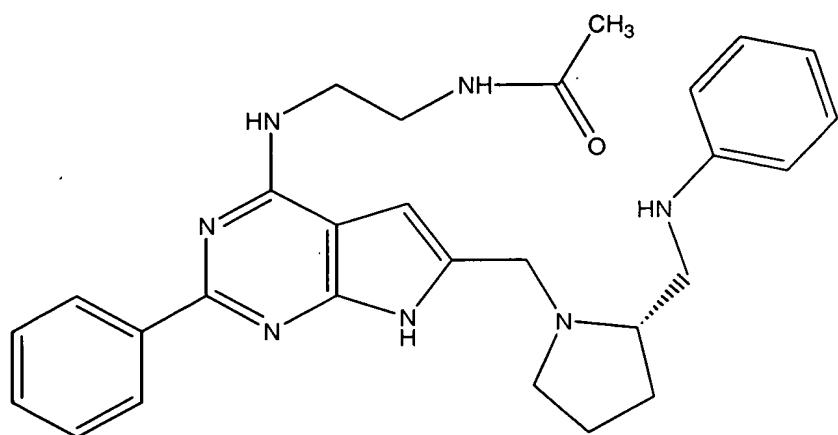
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

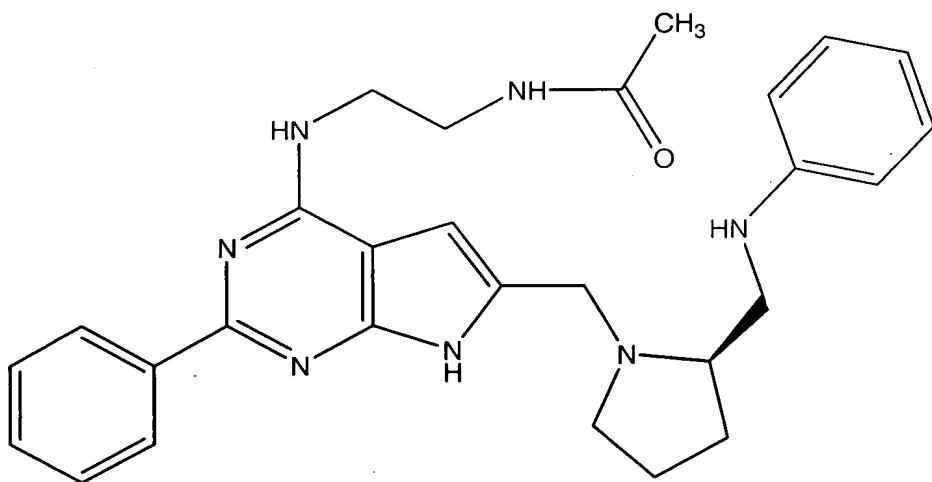
Filed : December 1, 2000

Page 13

92. (Currently amended) The compound of claim 76, having the structure:



93. (Currently amended) The compound of claim 92, having the structure:



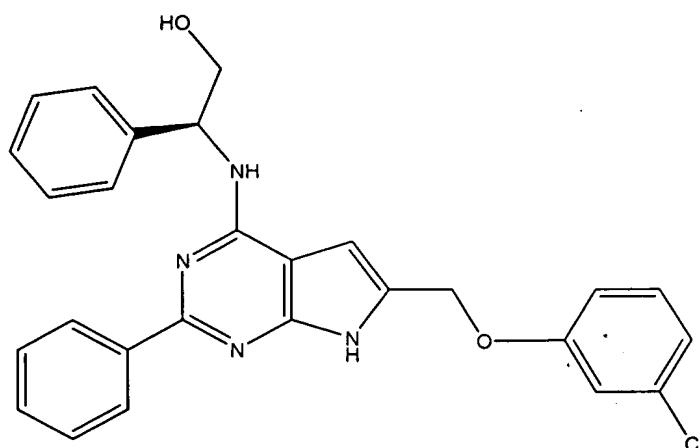
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

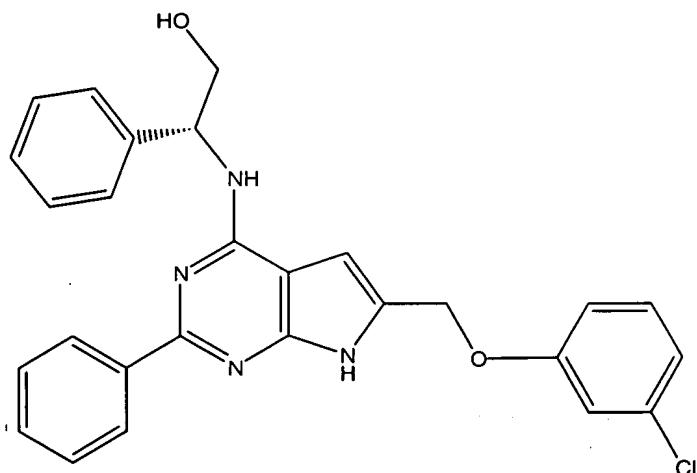
Filed : December 1, 2000

Page 14

94. (Currently amended) The compound of claim 76, having the structure:



95. (Currently amended) The compound of claim 94, having the structure:



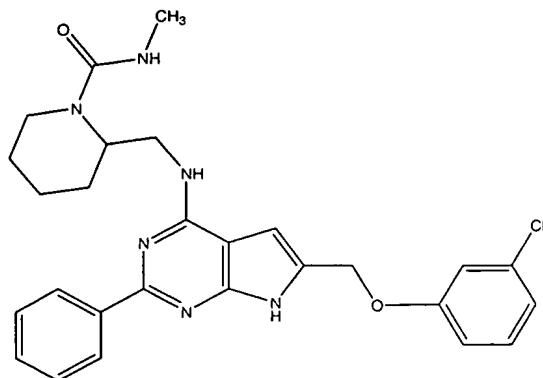
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

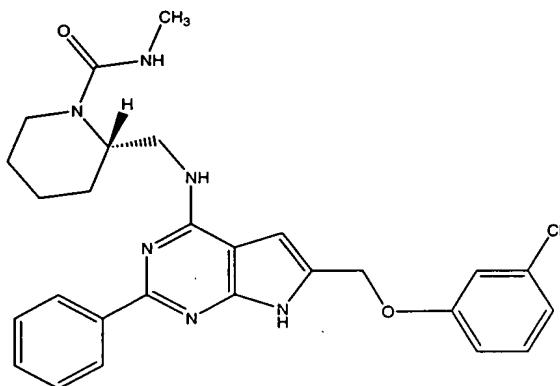
Filed : December 1, 2000

Page 15

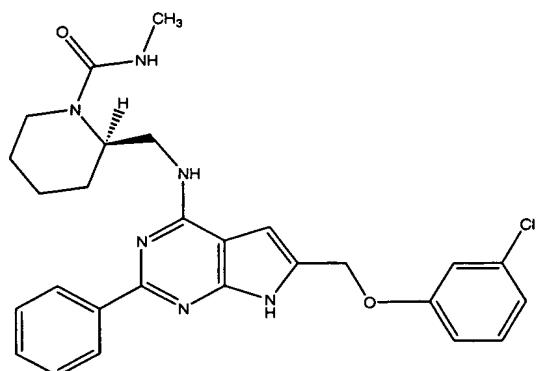
96. (Currently amended) The compound of claim 76, having the structure:



97. (Currently amended) The compound of claim 96, having the structure:



98. (Currently amended) The compound of claim 96, having the structure:



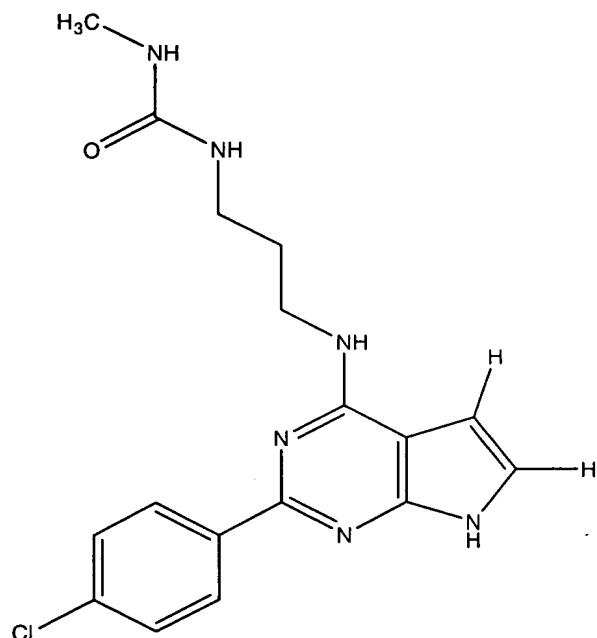
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 16

99. (Currently amended) A compound having the structure:



100. (Previously presented) A method for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is myocardial ischemia, bronchitis, or bronchoconstriction.

101. (Previously presented) The method of claim 100, wherein the subject is a mammal.

102. (Previously presented) The method of claim 101, wherein the mammal is a human.

103. (Previously presented) A prodrug of the compound of claim 76 or 99, wherein the prodrug is metabolized *in vivo* by a

Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 17

human subject to an active drug which selectively inhibits the A3 adenosine receptor wherein the prodrug is an ester of an alcohol or carboxylic acid group, if such a group is present in the compound; an acetal or ketal of an alcohol group, if such a group is present in the compound; an N-Mannich base or an imine of an amine group, if such a group is present in the compound; or a Schiff base, oxime, acetal, enol ester, oxazolidine, or thiazolidine of a carbonyl group, if such a group is present in the compound.

104. (Previously presented) The prodrug of claim 103, wherein the prodrug is water-soluble.

105. (Currently amended) The prodrug of claim 103, wherein said prodrug is metabolized in vivo by esterase catalyzed hydrolysis the prodrug is an ester of an alcohol group.

106. (Previously presented) A pharmaceutical composition comprising the prodrug of claim 103 and a pharmaceutically acceptable carrier.

107. (Previously presented) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is an ophthalmic formulation.

108. (Previously presented) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 18

109. (Previously presented) The pharmaceutical composition of claim 106, wherein said pharmaceutical composition is a systemic formulation.

110. (Currently amended) A method for inhibiting the activity of an A3 adenosine receptor in a cell ~~that is subjected to abnormal stimulation of the A3 adenosine receptor~~, which comprises contacting the cell with a compound of claim 76 or 99, so as to inhibit the activity of the A3 adenosine receptor.

Claims 111-113. (Canceled)

114. (Previously presented) A method for treating a respiratory disorder associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound of claim 76 or 99, so as to thereby treat the respiratory disorder in the subject, wherein the respiratory disorder is asthma, chronic obstructive pulmonary disease, allergic rhinitis or an upper respiratory disorder.

115. (Previously presented) The method of claim 114, wherein the subject is a human.

116. (Previously presented) A method for treating inflammation of the eye associated with an A3 adenosine receptor in a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of the compound of claim 76 or 99 so as to thereby treat the inflammation of the eye in the subject.

117. (Previously presented) A method for treating a disease

Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 19

associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is associated with mast cell degranulation.

118. (Previously presented) The method of claim 117 wherein the subject is human.

119. (Previously presented) A method for treating a disease associated with an A3 adenosine receptor in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of claim 76 or 99 so as to thereby treat the disease associated with the A3 adenosine receptor in the subject, wherein the disease associated with the A3 adenosine receptor is asthma, glaucoma, retinopathy, ocular ischemia, or macular degeneration.

120. (Previously presented) The method of claim 119, wherein the subject is human.

121. (Previously presented) The method of claim 119, wherein the disease is asthma.

122. (Previously presented) The method of claim 119, wherein the disease is glaucoma.

123. (Previously presented) A combination therapy for glaucoma, comprising the compound of claim 76 or 99, and a prostaglandin agonist, $\beta 2$ agonist, or a muniscrinic antagonist.

Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 20

124. (Currently amended) A pharmaceutical composition comprising a ~~therapeutically effective amount of~~ the compound of claim 76 or 99 and a pharmaceutically acceptable carrier.

125. (Canceled)

126. (Previously presented) The pharmaceutical composition of claim 125, wherein said gastrointestinal disorder is diarrhea.

127. (Previously presented) The pharmaceutical composition of claim 125, wherein said respiratory disorder is asthma, allergic rhinitis, or chronic obstructive pulmonary disease.

128. (Previously presented) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is an ophthalmic formulation.

129. (Previously presented) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is an periocular, retrobulbar or intraocular injection formulation.

130. (Previously presented) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is a systemic formulation.

131. (Previously presented) The pharmaceutical composition of claim 124, wherein said pharmaceutical composition is a surgical irrigating solution.

132. (Canceled)

Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 21

133. (Currently amended) A method of preparing the compound of
claim 76, comprising the steps of

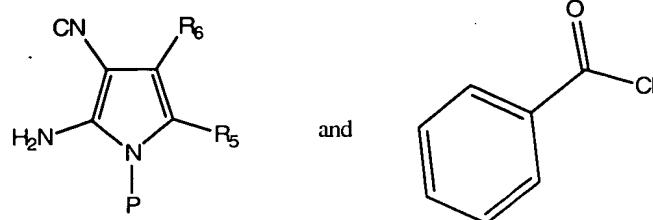
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

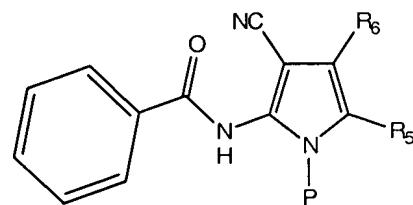
Filed : December 1, 2000

Page 22

a) reacting

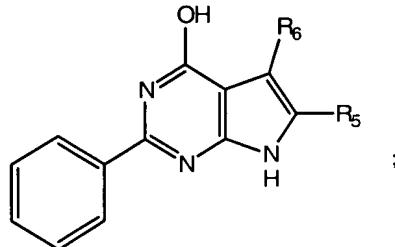


to provide

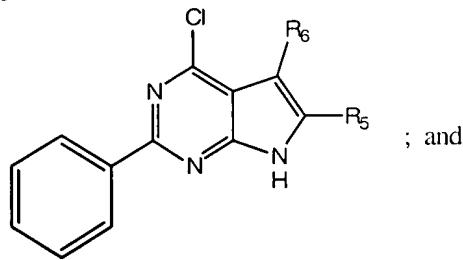


wherein P is a removable protecting group;

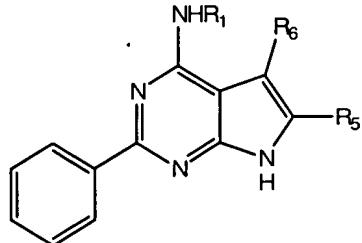
b) treating the product of step a) under cyclization conditions with acid in the presence of solvent to provide



c) treating the product of step b) under suitable conditions with a chlorinating agent to provide



d) treating the chlorinated product of step c) with NH₂R₁ to provide



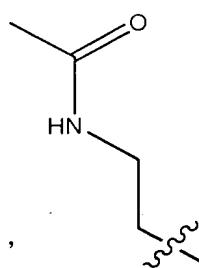
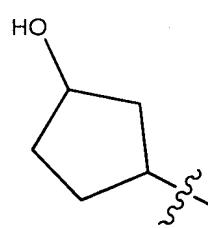
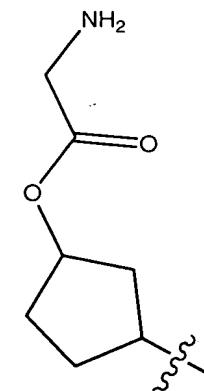
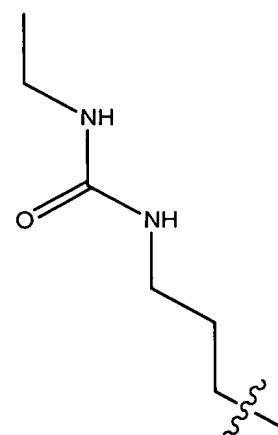
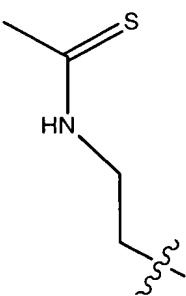
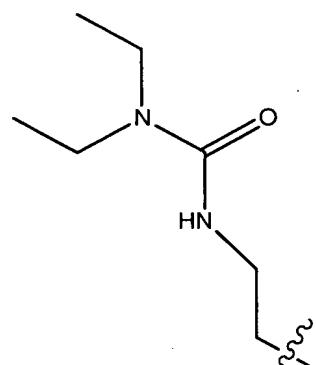
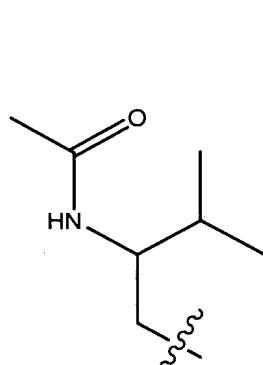
Applicants: Arlindo L. Castelhano et al.

Serial No.: 09/728,616

Filed : December 1, 2000

Page 23

wherein R₁ is 3-hydroxy cyclopentyl ethylamino carbonylamino propyl, N,N-diethylamino carbonylamino ethyl, thioacetamido ethyl, 3-amino acetyloxy cyclopentyl, 3-hydroxy cyclopentyl, 2-pyrrolyl carbonyl aminoethyl, 2-imidazolidinone ethyl, 1-aminocarbonyl-2-methyl propyl, 1-aminocarbonyl-2-phenyl ethyl, 3-hydroxy azetidino, 2-imidazolyl ethyl, acetamido ethyl, 1-(R)-phenyl-2-hydroxyethyl, or N-methylaminocarbonyl pyridyl-2-methyl,

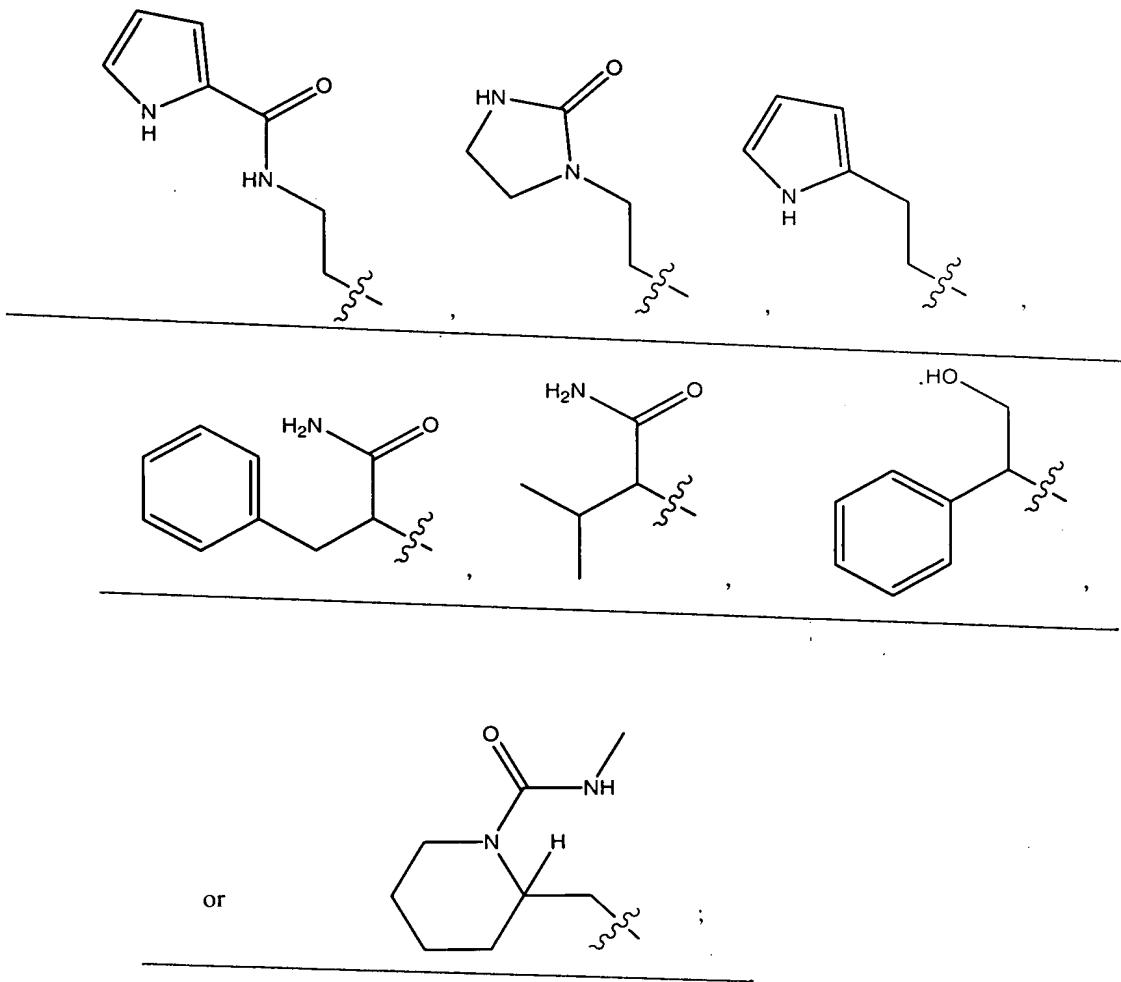


Applicants: Arlindo L. Castelhano et al.

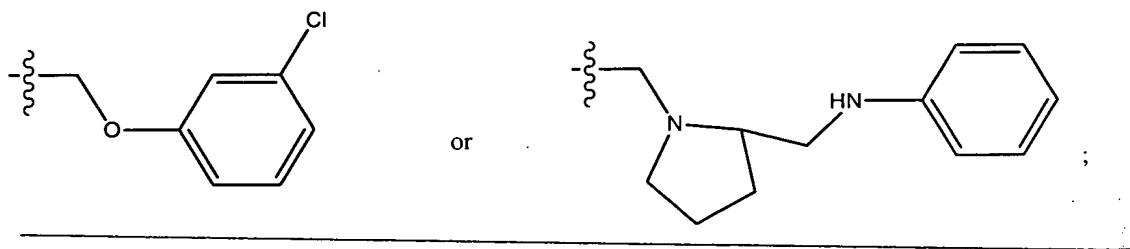
Serial No.: 09/728,616

Filed : December 1, 2000

Page 24



wherein R_5 is and R_6 are independently H, substituted or
unsubstituted alkyl, or aryl. H, CH₃, phenyl.



Applicants: Arlindo L. Castelhano et al.

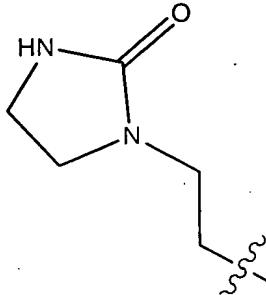
Serial No.: 09/728,616

Filed : December 1, 2000

Page 25

wherein R₆ is H or CH₃.

and wherein when R₁ is



R₅ is phenyl.

134. (New) The method of claim 133, wherein the acid of step b) is sulfuric acid, the solvent of step b) is methanol, and the chlorinating agent of step c) is POCl₃.

135. (New) The method of claim 134, wherein step b) further comprises treating the compound with polyphosphoric acid.